

06-26-00

A

PATENT
Attorney Docket No. MEDIN1400

06/23/00
1c857 U.S. PTO

☒ NEW PATENT APPLICATION
☐ CONTINUATION-IN-PART
☐ DIVISIONAL

ASSISTANT COMMISSIONER
FOR PATENTS
Box Patent Application
Washington, D.C. 20231

CERTIFICATE OF MAILING BY "EXPRESS MAIL"	
"EXPRESS MAIL" MAILING LABEL NO	EL617040291US
DATE OF DEPOSIT	06/23/2000
I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 C.F.R. 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231	
Mikhail BAYLEY	
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)	
Mikhail Bayley	
SIGNATURE OF PERSON MAILING PAPER OR FEE	

1c832 U.S. PTO
06/23/00

Sir:

Transmitted herewith for filing is the new patent application of

Inventor(s): Ching-San Lai and Tingmin Wang

For: **PROTECTED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR**

Enclosed are:

- ☒ 44 pages of the Specification, which includes 6 pages of the claims.
☒ 1 page of the Abstract;
☒ 3 sheets of drawing(s) ☒ Formal; ___ Informal;
☒ A Declaration;
☒ Power of Attorney By Assignee;
☒ An assignment of the invention with cover sheet to MEDINOX, INC.; and
☒ A verified statement to establish small entity status under 37 C.F.R. 1.9 and 37 C.F.R. 1.27.

FULL NAME OF FIRST INVENTOR	LAST NAME: Lai	FIRST NAME: Ching-San	MIDDLE NAME: None
CITIZENSHIP	STATE OR FOREIGN COUNTRY: United States		
POST OFFICE ADDRESS	POST OFFICE ADDRESS: 209 Lolita Street	CITY AND STATE: Encinitas, CA	ZIP CODE: 92024
FULL NAME OF SECOND INVENTOR	LAST NAME: Wang	FIRST NAME: Tingmin	MIDDLE NAME: None
CITIZENSHIP	STATE OR FOREIGN COUNTRY: People's Republic of China		
POST OFFICE ADDRESS	POST OFFICE ADDRESS: 585 Sonoma Street	CITY AND STATE: San Marcos, CA	ZIP CODE: 92069

In re Application of:
Lai and Wang
Application No.: unassigned
Filed: June 23, 2000
Page 2

PATENT
Attorney Docket No.: MEDIN1400

The filing fee has been calculated as shown below:

For	Number Filed		Number Extra		Rate			Fee	
					Small Entity	Other Entity		Small Entity	Other Entity
Total Claims	33	=	13		\$9	\$18	=	\$117.00	\$ 0
Independent Claims	7	=	4		\$39	\$78	=	\$156.00	0
Multiple Dependent Claims Presented: ___ Yes <u>X</u> No					\$130	\$260			0
BASIC FEE					\$345	\$690		\$345.00	\$ 0
TOTAL FEE								\$618.00	\$ 0

— The payment of the filing fee is to be deferred until the Declaration is filed. Do not charge our deposit account.

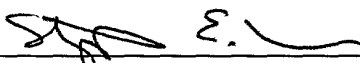
X The Commissioner is authorized to charge payment in the amount of \$658.00; \$345.00 for the filing fee, \$273.00 for the additional independent claims and \$40.00 for the recordation of one (1) assignment and any other fees associated with this communication or credit any overpayment to Deposit Account No. 07-1895. A duplicate copy of this sheet is enclosed.

X Any additional filing fees required under 37 C.F.R. 1.16.

X Any patent application processing fees under 37 C.F.R. 1.17.

Respectfully submitted,

Date: 6/23/00


Stephen E. Reiter
Attorney for Applicant
Registration No. 31,192
Telephone: 858-677-1409
Facsimile: 858-677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, CA 92121-2189

Attorney Docket No. MEDIN1400
Applicant or Patentee: Lai and Wang
Serial No. or Patent No.:
Filed or Issued: June 23, 2000
Title: PROTECTED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES
THEREFOR

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 C.F.R. §§ 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

- ☐ the owner of the small business concern identified below:
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN MEDINOX, INC.
ADDRESS OF CONCERN 11575 Sorrento Valley Road, Suite 201
San Diego, California 92121

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 C.F.R. §121.3-18 and reproduced in 37 C.F.R. § 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled **PROTECTED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR** by inventors **Ching-San Lai and Tingmin Wang** described in:

- ☒ the specification filed herewith
☐ Based on Application Serial No. _____, filed herewith.
☐ Patent No. _____, issued _____

I authorize and request insertion of the serial number of the application when officially known.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above-identified invention.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 C.F.R. §1.9(d) or by any concern which would not qualify as a small business concern under 37 C.F.R. §1.9(d) or a nonprofit organization under 37 C.F.R. §1.9(e).

NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities (37 C.F.R. §1.27).

Full Name _____
Address _____
☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization
Full Name _____
Address _____
☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate (37 C.F.R. '1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Ching-San Lai
TITLE OF PERSON OTHER THAN OWNER President and Chief Executive Officer
ADDRESS OF PERSON SIGNING _____
SIGNATURE [Signature] DATE 6/23/00

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"EXPRESS MAIL LABEL NUMBER" EL617040291US

DATE OF DEPOSIT 06/23/2000

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER OF PATENTS, BOX PATENT APPLICATION, WASHINGTON, D.C. 20231

Mikhail Bayley
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER)

Mikhail Bayley
(SIGNATURE OF PERSON MAILING PAPER OR FEE)

APPLICATION

for

UNITED STATES LETTERS PATENT

on

PROTECTED FORMS OF PHARMACOLOGICALLY
ACTIVE AGENTS AND USES THEREFOR

by

Tingmin Wang and Ching-San Lai

Sheets of Drawings: Three

Docket No.: MEDIN1400

Attorneys

Gray Cary Ware & Freidenrich
4365 Executive Drive, Suite 1600
San Diego, California 92121-2189

062390 062300

Protected Forms of Pharmacologically

Active Agents and Uses Therefor

FIELD OF THE INVENTION

5 The present invention relates to novel forms of pharmacologically active agents, and methods for the preparation and use thereof. In a particular aspect of the invention, methods are provided for treating pathological conditions with a protected form of one or more pharmacologically active agents, thereby reducing the occurrence of side-effects caused thereby.

BACKGROUND OF THE INVENTION

10 Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., naproxen, aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:1000-1016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307-319 (1991); and J. Bjarnason et al., in Gastroenterol. 104:1832-1847 (1993)).

20 There are two major ulcerogenic effects of NSAIDs: (1) irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow-release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically significant side effects, including perforation and bleeding (see, for example, D. Y.

Graham et al., in Clin. Pharmacol. Ther. 38:65-70 (1985); and J. L. Carson, et al., in Arch. Intern. Med., 147:1054-1059 (1987)).

It is well recognized that aspirin and other NSAIDs exert their pharmacological effects through the non-selective inhibition of cyclooxygenase (COX) enzymes, thereby blocking prostaglandin synthesis (see, for example, J. R. Van in Nature, 231:232-235 (1971)). There are two types of COX enzymes, namely COX-1 and COX-2. COX-1 is expressed constitutively in many tissues, including the stomach, kidney, and platelets, whereas COX-2 is expressed only at the site of inflammation (see, for example, S. Kargan et al. in Gastroenterol., 111:445-454 (1996)). The prostagladins derived from COX-1 are responsible for many of the physiological effects, including maintenance of gastric mucosal integrity.

Many attempts have been made to develop NSAIDs that only inhibit COX-2, without impacting the activity of COX-1 (see, for example, J.A. Mitchell et al., in Proc. Natl. Acad. Sci. USA 90:11693-11697 (1993); and E.A. Meade et al., in J. Biol. Chem., 268:6610-6614 (1993)). There are several NSAIDs presently on the market (e.g., rofecoxib and celecoxib) that show marked selectivity for COX-2 (see, for example, E. A. Meade, supra.; K. Glaser et al., in Eur. J. Pharmacol. 281:107-111 (1995) and Kaplan-Machlis, B., and Klostermeyer, BS in Ann Pharmacother. 33:979-88, (1999)). These drugs appear to have reduced gastrointestinal toxicity relative to other NSAIDs on the market.

On the basis of encouraging clinical as well as experimental data, the development of highly selective COX-2 inhibitors appears to be a sound strategy to develop a new generation of anti-inflammatory drugs. However, the physiological functions of COX-1 and COX-2 are not always well defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to inflammation, pain and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including the initiation and maintenance of labor and in the regulation of bone resorption (see, for example, D. M.

Slater et al., in Am. J. Obstet. Gynecol., 172:77-82 (1995); and Y. Onoe et al., in J. Immunol. 156:758-764 (1996)), thus inhibition of this pathway may not always be beneficial. Considering these points, highly selective COX-2 inhibitors may produce additional side effects above and beyond those observed with standard NSAIDs, therefore such inhibitors may not be highly desirable.

Accordingly, there is still a need in the art for modified forms of NSAIDs which cause a reduced incidence of side-effects, relative to the incidence of side-effects caused by such pharmacologically active agents in unmodified form.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a new class of modified NSAIDs which cause a much lower incidence of side-effects than are typically observed with unmodified NSAIDs due to the protective effects imparted by modifying the NSAIDs as described herein.

There are a number of advantages provided by modified NSAIDs according to the invention including:

- (i) reduced irritant effects (e.g., contact irritation) of NSAIDs, and
- (ii) enhanced tissue delivery of the drug as a result of a decrease in net charges on the molecule, particularly for acidic NSAIDs such as naproxen, aspirin, diclofenac and ibuprofen, thereby reducing the quantity of material which must be delivered to achieve an effective dosage.

In accordance with the present invention, cleavage of the modified NSAIDs described herein from the modified group appended thereto releases the pharmaceutically active agent.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the total length of intestinal ulcers measured after three daily doses of NSAID in unfasted male Sprague-Dawley rats (150-200 g) treated with vehicle, naproxen or equimolar invention composition (compound 19). * P < 0.05 by unpaired t-test.

Figure 2 illustrates the total length of intestinal ulcers measured after 14 daily doses of NSAID in unfasted male Sprague-Dawley rats (150-200 g) treated with vehicle (bar 7), three doses of naproxen (bar 1: 50 mg/kg, bar 2: 45 mg/kg, bar 3: 40 mg/kg), or three equimolar doses of invention composition (compound 19) (bars 4-6). * P < 0.05 by unpaired t-test vs. corresponding dose of naproxen.

Figure 3 illustrates the inhibition of paw volume increases in the uninjected feet of Lewis male rats in which arthritis was induced by intradermal injection of adjuvant into the footpad. Rats were injected on day 0 and treated once daily from days 8 to 15 with vehicle, naproxen (10 mg/kg), or invention composition (compound 19) at equivalent dose. Paw volumes were measured with a Plethysmometer on days 5 and 15. Closed circles = naproxen; squares = invention composition.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds comprising a modified NSAID, wherein the NSAID is covalently attached either directly or through a linker molecule to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety. Invention compounds have the structure:

X-L-Z

wherein:

X = a non-steroidal anti-inflammatory drug (NSAID),

L = an optional linker/spacer, and

5 Z = a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

NSAIDs contemplated for modification in accordance with the present invention include acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen,
 10 others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (Iodine), fenoprofen calcium (nalfon), flurbiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), carprofen, indoprofen, ketorolac tromethamine (toradol), magnesium salicylate (Doan's, magan, mobidin, others), meclofenamate sodium
 15 (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like. Presently preferred NSAIDs employed in the practice of the invention include naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, carprofen,
 20 and the like.

Invention compounds can be readily prepared in a variety of ways either by direct reaction of NSAIDs with the sulfur-containing functional group or indirectly through a suitable linker molecule.

25

The components of invention compositions are directly or indirectly covalently attached employing a variety of linkages (including an optional linker), e.g., ester linkages, disulfide linkages, amide linkages, imine linkages, enamine linkages, ether linkages, thioether linkages, imide linkages, sulfate ester linkages, sulfonate ester
 30 linkages, sulfone linkages, sulfonamide linkages, phosphate ester linkages, carbonate linkages, O-glycosidic linkages, S-glycosidic linkages, and the like. Such linkages can

be accomplished using standard synthetic techniques as are well known by those of skill in the art, either by direct reaction of the starting materials, or by incorporating a suitable functional group on the starting material, followed by coupling of the reactants.

5 When the pharmacologically active agents contemplated for use herein contain suitable functionality thereon, e.g., hydroxy, amino, carboxy, and the like, invention modified NSAIDs can be prepared by direct linkage between the two agents. Alternatively, the NSAIDs can be functionalized so as to facilitate linkage between the two agents. When present, linker/spacer L has the following structure:

10 -W-R-

 wherein:

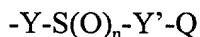
 R is optional, and when present is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, 15 substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

 W is ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, imine, enamine, or the like.

20 Functional groups contemplated by the present invention are sulfur-based. Examples of suitable sulfur-containing functional groups include sulfonate, reverse sulfonate, sulfonamide, reverse sulfonamide, sulfone, sulfinde, reverse sulfinde, and the like. In a particular aspect of the invention, the sulfur-based moiety is sulfonate or reverse sulfonate. In a particularly preferred aspect of the invention, the sulfonate is an 25 optionally substituted aromatic sulfonate such as tosylate or brosylate.

 Other preferred sulfur-based functional groups contemplated by the present invention include sulfones. Preferably, the sulfone is an optionally substituted alkyl or aromatic sulfone.

In one aspect of the invention, Z may have the following structure:



wherein:

5 each of Y and Y' are optionally present, and when present are independently –O- or –NR'-, wherein R' is H or an optionally substituted hydrocarbyl moiety;

n is 1 or 2, and

Q is H or an optionally substituted hydrocarbyl moiety.

10

As employed herein, "hydrocarbyl" embraces alkyl, substituted alkyl, oxyalkyl, substituted oxyalkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, monocyclic heterocyclic, substituted monocyclic heterocyclic, monocyclic aromatic, monosubstituted monocyclic aromatic, or the like.

15

As employed herein, "alkyl" refers to hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkyl" comprises alkyl groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano, nitro, nitro, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfuryl, and the like.

20

25 As employed herein, "oxyalkyl" refers to the moiety –O-alkyl-, wherein alkyl is as defined above, and "substituted oxyalkyl" refers to oxyalkyl groups further bearing one or more substituents as set forth above.

25

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

30

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "monocyclic aromatic" refers to aromatic groups having in the range of 5 up to 7 carbon atoms and "monosubstituted monocyclic aromatic" refers to aromatic groups further bearing one of the substituents set forth above.

As employed herein, "alkylene" refers to divalent hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkylene" comprises alkylene groups further bearing one or more substituents as set forth above.

As employed herein, "cycloalkylene" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkylene" refers to cycloalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "oxyalkylene" refers to the moiety -O-alkylene-, wherein alkylene is as defined above, and "substituted oxyalkylene" refers to oxyalkylene groups further bearing one or more substituents as set forth above.

5

As employed herein, "alkenylene" refers to divalent, straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenylene" refers to alkenylene groups further bearing one or more substituents as set forth above.

10

As employed herein, "alkynylene" refers to divalent straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynylene" refers to alkynylene groups further bearing one or more substituents as set forth above.

15

As employed herein, "arylene" refers to divalent aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted arylene" refers to arylene groups further bearing one or more substituents as set forth above.

20

As employed herein, "alkylarylene" refers to alkyl-substituted arylene groups and "substituted alkylarylene" refers to alkylarylene groups further bearing one or more substituents as set forth above.

25

As employed herein, "arylalkylene" refers to aryl-substituted alkylene groups and "substituted arylalkylene" refers to arylalkylene groups further bearing one or more substituents as set forth above.

30

As employed herein, "arylalkenylene" refers to aryl-substituted alkenylene groups and "substituted arylalkenylene" refers to arylalkenylene groups further bearing one or more substituents as set forth above.

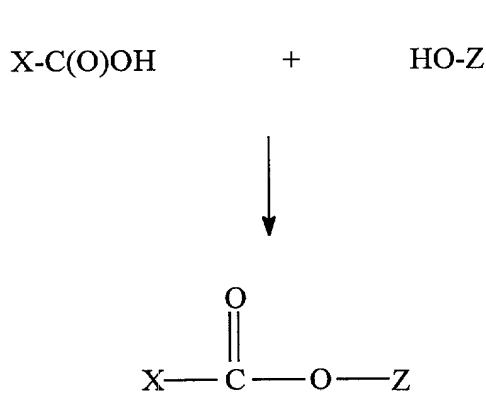
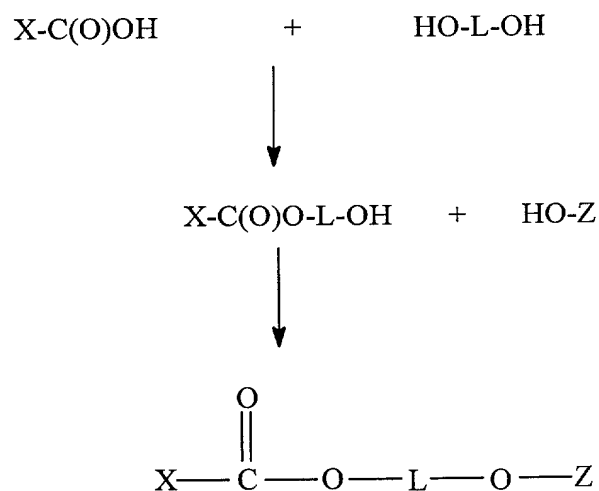
As employed herein, "arylalkynylene" refers to aryl-substituted alkynylene groups and "substituted arylalkynylene" refers to arylalkynylene groups further bearing one or more substituents as set forth above.

5 Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, 10 arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, 15 stroke, cancers (e.g., breast, melanoma, carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic 20 fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver 25 disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.

30 In accordance with another embodiment of the present invention, there are provided methods for the preparation of modified NSAIDs, said method comprising covalently attaching a NSAID to a sulfur-containing functional group containing an

optionally substituted hydrocarbyl moiety. The resulting compound provides a latent form of the pharmacologically active agent, releasing the biological activity thereof only when the compound is cleaved (e.g., by an esterase, amidase or other suitable enzyme).

- 5 As readily recognized by those of skill in the art, invention compounds can be prepared in a variety of ways. See, for example, Scheme 1, wherein NSAID, X, bearing a carboxylic moiety can be reacted either directly with the sulfur-containing functional group (Scheme 1a) or indirectly through a linker molecule (Scheme 1b).

10 **Scheme 1a****Scheme 1b**

Employing these general reaction schemes, invention modified NSAIDs can be prepared from a wide variety of pharmacologically active agents. See, for example, Examples 1-29 provided herein.

15

- In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of NSAIDs to a subject, said method comprising covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID prior to
- 20 administration to said subject.

5

10

15

20

25

30

NSAIDs may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention modified NSAIDs are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention modified NSAIDs may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention modified NSAIDs in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form

osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention modified NSAIDs are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention modified NSAIDs are mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Invention modified NSAIDs contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention modified NSAIDs with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of invention modified NSAIDs employed as described herein falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 10 μ g up to about 100 mg per kg body weight, and, preferably within the range of from 50 μ g to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μ g to about 100 mg per kg body weight, and, preferably, within the range of from 10 μ g to 10 mg per kg body weight.

In accordance with yet another embodiment of the present invention, there are provided improved methods for the treatment of a subject suffering from a pathological condition by administration thereto of a NSAID, the improvement comprising covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

Thus, invention method for the treatment of a subject afflicted with a pathological condition comprises administering to a subject an effective amount of a modified pharmacologically active agent,

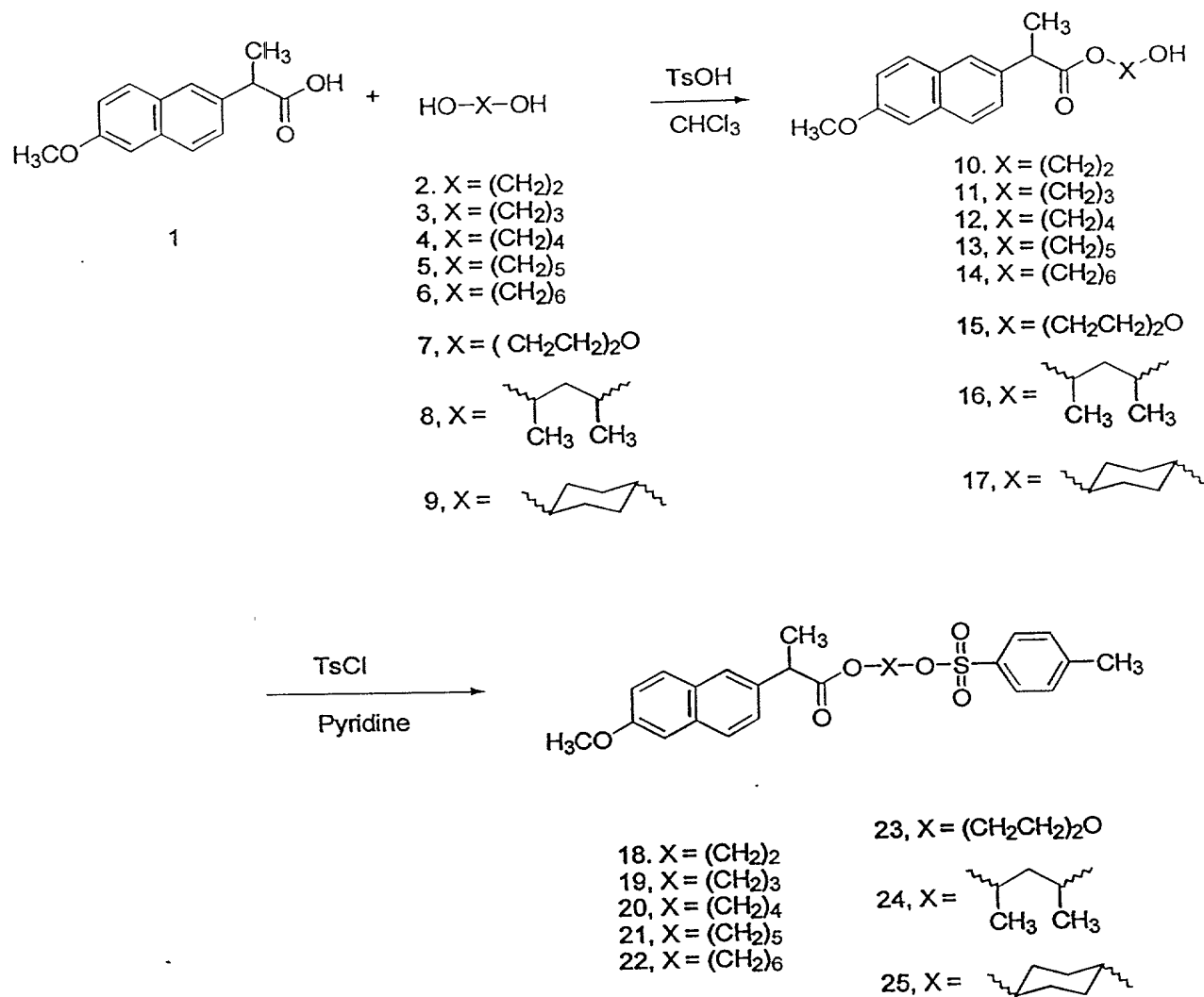
wherein said pharmacologically active agent is a NSAID, and is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

The invention will now be described in greater detail by reference to the following non-limiting examples.

The syntheses described in Examples 1-8 are outlined in Scheme 2.

Scheme 2



Example 1

Compound 10 (Scheme 2). A mixture of Naproxen (**1**) (23 g, 0.1 mol), ethylene glycol (**2**) (27.9 ml, 0.5 mol) and toluenesulfonic acid (TsOH) (1.27g, 6.7 mmol) in CHCl₃ was heated to reflux for 4 h. The reaction solution was washed with water, 10% Na₂CO₃ solution and water. The organic layer was dried (Na₂SO₄) and the solvent was evaporated. The residue was purified by crystallization from CH₂Cl₂ and hexanes to give 25.7g (94%) of the compound **10** as a white crystal ; ¹H NMR (CDCl₃) δ 1.59 (d, 3H), 1.62 (br, 1H, ex D₂O), 3.74 (t, 2H), 3.90 (q, 1H), 3.91 (s, 3H), 4.21 (t, 2H), 7.11 (m, 2H), 7.39 (d, 1H), 7.69 (m, 3H); ¹³C NMR (CDCl₃) d 18.7, 45.6, 55.5, 61.4, 66.6, 105.8, 119.3, 126.1, 126.2, 127.5, 129.1, 129.5, 133.9, 135.7, 157.9, 175.2; MS (ESI) *m/z* 273 (M-1).

Compound 18 (Scheme 2). To a solution of compound **10** (24.5g, 89 mmol) in 100 ml of pyridine was added tosyl chloride (TsCl) (34.1g, 179 mmol). The resulting solution was stirred at 0° C for 2.5h. The reaction solution was then poured into 300 ml of water and then 200 ml of ether was added. The layers were separated and the organic phase was washed with water (300 x 5) and dried (Na₂SO₄). After the solvent was evaporated, the residue was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give 35.1g (92%) of the pale yellow oil; ¹H NMR (CDCl₃) δ 1.55(d, 3H), 2.40 (s, 3H), 3.91 (q, 1H), 4.18 (m, 4H), 7.12 (m, 2H), 7.24 (m, 2H), 7.37 (d, 1H), 7.66 (d, 1H), 7.70 (m, 4H); MS (ESI) *m/z* 429 (M+1).

Example 2

Compound 11 (Scheme 2). Compound **11** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and 1,3-propanediol (**3**). The resulting compound **11** was purified by crystallization from dichloromethane and hexanes with a 92% yield. ¹H NMR (CDCl₃) δ 1.59 (d, 3H), 1.78 (m, 2H), 1.87 (br, 1H, D₂O ex), 3.53 (t, 2H), 3.87 (q, 1H), 3.91 (s, 3H), 4.23 (t, 2H),

7.11 (d, 1H), 7.15 (m, 1H), 7.41 (q, 1H), 7.66 (d, 1H), 7.69 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (CDCl_3) δ 18.6, 31.8, 45.7, 55.5, 59.2, 61.9, 77.0, 77.2, 77.5, 105.8, 119.2, 126.1, 126.3, 127.4, 129.1, 129.4, 133.9, 135.7, 157.8, 175.3; and MS (ESI) m/z 289.4 (M+1).

5

Compound 19 (Scheme 2). Compound **19** was prepared as described above for the preparation of compound **18**, this time employing compound **11** and TsCl.

Compound **19** was purified by crystallization from ether and hexane with an yield of 95%; ^1H NMR (CDCl_3) δ 1.54 (d, 3H), 1.91 (m, 2H), 2.42 (s, 3H), 3.79 (q, 1H), 3.92 (s, 3H), 3.99 (t, 2H), 4.10 (t, 2H), 7.11 d, 1H), 7.15 (q, 1H), 7.26 (d, 2H), 7.34 (d, 2H), 7.62(d, 1H), 7.70 (m, 4H); ^{13}C NMR (CDCl_3) δ 18.5, 21.8, 28.4, 45.5, 55.5, 60.6, 66.9, 105.8, 119.2, 126.0, 126.3, 127.4, 128.0, 129.1, 129.5, 130.1, 133.1, 133.9, 135.6, 145.0, 157.9, 174.5; MS (ESI) m/z 421.1 (M-1).

15

Example 3

Compound 12 (Scheme 2). Compound **12** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and 1,4-butanediol (**4**). Compound **12** was purified by crystallization from dichloromethane and hexanes with a 90% yield; ^1H NMR (CDCl_3) δ 1.48 (m, 2H), 1.59 (d, 3H), 1.64 (m, 2H), 1.85 (s, 1H, D_2O , ex), 3.52 (t, 2H), 3.85 (q, 1H), 3.89 (s, 3H), 4.10 (t, 2H), 7.10-7.15 (m, 2H), 7.42 (d, 1H), 7.66-7.7- (m, 3H); MS (ESI) m/z 325.4 (M+ Na).

20

Compound 20 (Scheme 2). Compound **20** was prepared as described above for the preparation of compound **18**, this time employing compound **12** and TsCl. The compound **20** was purified by crystallization from ether and hexane with an yield of 93%; ^1H NMR (CDCl_3) δ 1.55 (d, 3H), 1.53-1.62 (m, 4H), 2.43 (s, 3H), 3.82 (q, 1H), 3.92 (s, 3H), 3.94 (m, 2H), 4.02 (m, 2H), 7.11-7.15 (m, 2H), 7.30 (d, 2h), 7.38 (d, 1H), 7.64 (d, 1H), 7.70 (d, 2H), 7.75 (d, 2H); MS (ESI) m/z 457.5 (M+1).

25

Example 4

Compound 13 (Scheme 2). Compound **13** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and 1,5-pentenediol (**5**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated under high vacuum to give a quantitative yield of the compound **13**. The compound was used to make compound **21** without further purification; ^1H NMR (CDCl_3) δ 1.28 (m, 2H), 1.46 (m, 2H), 1.55 (d, 3H), 1.59 (m, 2H), 3.51 (t, 2H), 3.85 (q, 1H), 3.91 (s, 3H), 4.09 (t, 2H), 7.11-7.15 (m, 2H), 7.40 (q, 1H), 7.66-7.70 (m, 3H); MS (ESI) m/z 317.5 (M+1).

Compound 21 (Scheme 2). Compound **21** was prepared as described above for the preparation of compound **18**, this time employing compound **13** and TsCl. Compound **21** was purified by crystallization from ether and hexane with a 95% yield; ^1H NMR (CDCl_3) δ 1.24 (m, 2H), 1.48-1.58 (m, 4H), 1.59 (d, 3H), 2.43 (s, 3H), 3.84 (q, 1H), 3.89 (t, 2H), 3.91 (s, 3H), 4.01 (t, 2H), 7.11-7.15 (m, 2H), 7.32 (q, 2H), 7.39 (q, 1H), 7.65 (d, 1H), 7.70 (m, 2H), 7.75 (d, 2H); MS (ESI) m/z 471.7 (M+1).

Example 5

Compound 14 (Scheme 2). Compound **14** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and 1,6-hexanediol (**6**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **14** as a solid. The compound was used to make compound **22** without further purification; ^1H NMR (CDCl_3) δ 1.24 (m, 4H), 1.43 (m, 2H), 1.56 (d, 3H), 1.54 (m, 2H), 3.51 (t, 2H), 3.85 (q, 1H), 4.01 (m, 2H), 7.10-7.15 (m, 2H), 7.40 (q, 1H), 7.66-7.70 (m, 3H); MS (ESI) m/z 331.7 (M+1).

Compound 22 (Scheme 2). Compound **22** was prepared as described above for the preparation of compound **18**, this time employing compound **14** and TsCl. Compound **22** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give compound **22** as a pale yellow oil; The ^1H NMR

(CDCl₃) δ 1.12–1.22 (m, 4H), 1.46–1.52 (m, 4H), 1.57 (d, 3H), 2.43 (s, 3H), 3.84 (q, 1H), 3.92 (s, 3H), 3.93 (m, 2H), 4.03 (m, 2H), 7.11–7.77 (m, 10H); MS (ESI) *m/z* 485.6 (M+1).

5

Example 6

Compound 15 (Scheme 2). Compound **15** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and di(ethylene glycol) (**7**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **15**. The compound was used to make compound **23** without further purification; ¹H NMR (CDCl₃) δ 1.58 (d, 3H), 1.93 (br, 1H, D₂O ex), 3.43 (t, 2H), 3.59 (t, 2H), 3.62 (t, 2H), 3.89 (q, 1H), 3.90 (s, 3H), 4.25 (m, 2H), 7.11–7.15 (m, 2H), 7.40–7.42 (m, 1H), 7.70 (t, 3H); ¹³C NMR (CDCl₃) δ 18.7, 45.6, 55.5, 61.8, 64.0, 69.2, 72.4, 76.9, 77.2, 77.5, 105.7, 119.2, 126.2, 126.4, 127.3, 129.0, 133.9, 135.7, 157.9, 174.8; MS(ESI) *m/z* 319.3 (M+1).

15

Compound 23 (Scheme 2). Compound **23** was prepared as described above for the preparation of compound **18**, this time employing compound **15** and TsCl. Compound **23** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 93% yield. The ¹H NMR (CDCl₃) δ 1.58 (d, 3H), 2.41 (s, 3H), 3.43 (m, 2H), 3.48 (m, 2H), 3.84 (q, 1H), 3.86 (s, 3H), 3.94 (t, 2H), 4.10 (m, 2H), 7.10–7.13 (m, 2H), 7.29 (d, 2H), 7.39 (d, 1H), 7.65–7.75 (m, 5H); ¹³C NMR (CDCl₃) δ 18.6, 21.8, 45.5, 55.5, 63.9, 68.7, 69.27, 69.27, 105.8, 119.2, 126.2, 126.4, 127.4, 128.1, 129.0, 129.4, 129.9, 133.9, 145.0, 157.9, 174.7; MS (ESI) *m/z* 473.4 (M+1).

25

Example 7

Compound 16 (Scheme 2). Compound **16** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and 1,3-pentanediol (**8**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **15** with a 32% yield. The compound was used to make compound **24** without further purification; ¹H NMR, ¹³C

30

NMR and MS are consistent with the structure of compound **16**.

Compound 24 (Scheme 2). Compound **24** was prepared as described above for the preparation of compound **18**, this time employing compound **16** and TsCl. The compound **24** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 82% yield. The ^1H NMR, ^{13}C NMR and MS are consistent with the structure of compound **24**.

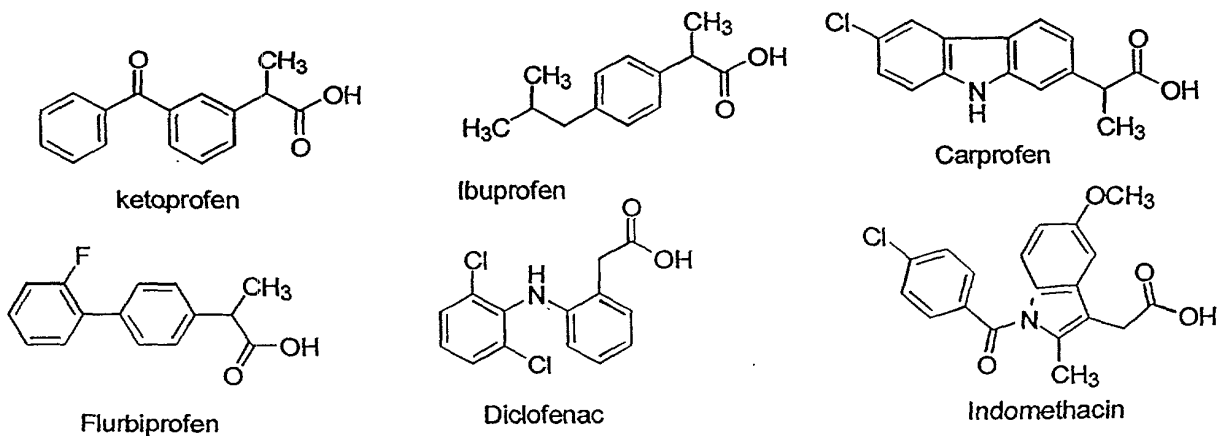
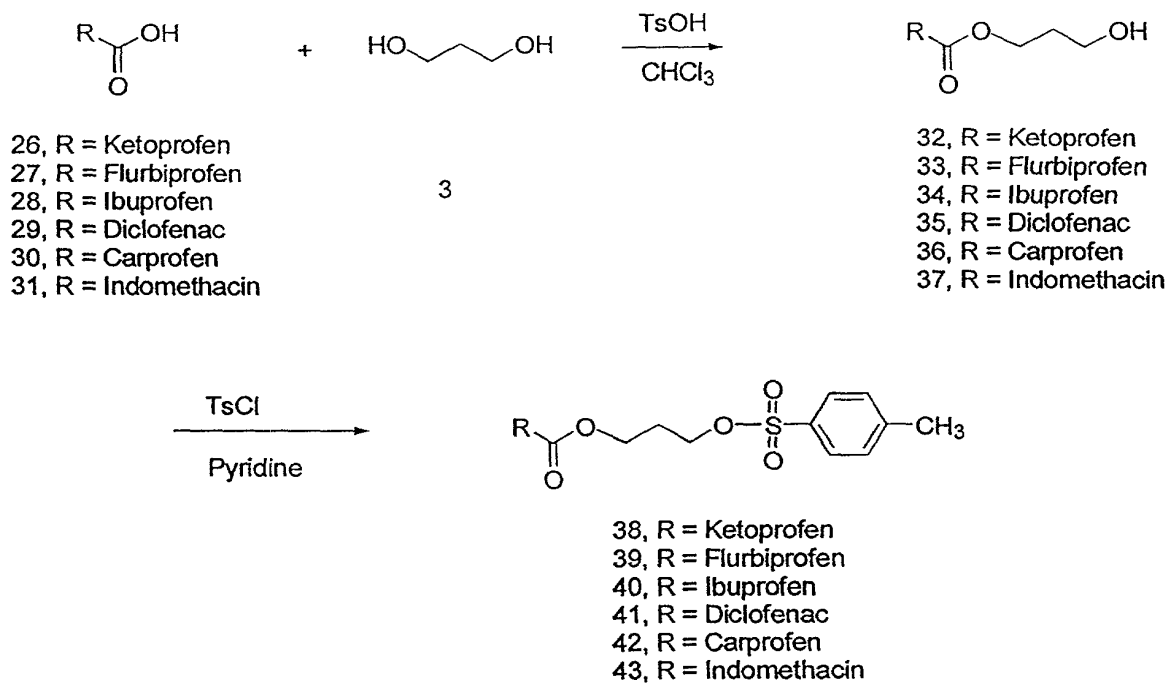
Example 8

Compound 17 (Scheme 2). Compound **17** was prepared as described above for the preparation of compound **10**, this time employing naproxen (**1**) and 1,4-cyclohexanediol (**8**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **17**. Compound **17** was used to make compound **25** without further purification; ^1H NMR (CDCl_3) δ 1.30-1.45 (m, 6H), 1.56 (d, 3H), 1.80-1.98 (m, 4H), 3.66 (m, 1H), 3.82 (q, 1H), 3.91 (s, 3H), 4.75 (m, 1H), 7.11 m, 2H), 7.39 (d, 1H), 7.65-7.70 (m, 3H); ^{13}C NMR (CDCl_3) 18.7, 28.2, 28.5, 32.1, 32.2, 45.9, 55.5, 68.9, 72.0, 76.9, 77.2, 77.5, 105.8, 119.1, 126.0, 126.4, 127.2, 129.1, 129.5, 133.8, 136.1, 157.8, 174.4; MS (ESI) m/z 351.4 (M + Na).

Compound 25 (Scheme 2). Compound **25** was prepared as described above for the preparation of compound **18**, this time employing compound **17** and TsCl. Compound **25** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 93% yield; ^1H NMR (CDCl_3) δ 1.50-1.84 (m, 11H), 2.43 (s, 3H), 3.80 (q, 1H), 3.92 (s, 3H), 4.51 (m, 1H), 4.78 (m, 1H), 7.10-7.15 (m 2H), 7.26-7.39 (m, 3H), 7.61-7.75 (m, 5H); MS (ESI) m/z 483.5 (M+H).

The syntheses described in Examples 9-14 are outlined in Scheme 3.

Scheme 3



Example 9

Compound 32 (Scheme 3). Compound **32** was prepared as described above for the preparation of compound **10**, this time employing ketoprofen (**26**) and 1,3-propanediol (**3**). Compound **32** was purified by column chromatography on a silica gel column using 200:1 CH₂Cl₂/MeOH as an eluent to give compound **32** with a 50% yield. ¹H NMR (CDCl₃) δ 1.55 (d, 3H), 1.82 (m 3H, 1H, D₂O ex), 3.58 (m, 2H), 3.82(m, 1H), 4.25 (m 2H), 7.44-7.82 (m, 9H); MS (ESI) *m/z* 313.5 (M+H).

Compound 38 (Scheme 3). Compound **38** was prepared as described above for the preparation of compound **18**, this time employing compound **32** and TsCl. Compound **38** was purified by column chromatography on a silica gel column using CH₂Cl₂ as an eluent to give the compound **38** as a colorless oil with a 81% yield; ¹H NMR (CDCl₃) δ 1.49 (d, 3H), 1.94 (m, 2H), 2.43 (s, 3H), 3.72 (q, 1H), 4.01 (t, 2H), 4.12 (m, 2H), 7.31-7.78 (m, 13H); MS (ESI) *m/z* 467.3 (M+H).

Example 10

Compound 33 (Scheme 3). Compound **33** was prepared as described above for the preparation of compound **10**, this time employing flurbiprofen (**27**) and 1,3-propanediol (**3**). After reaction, the reaction solution was washed in water and the reaction solvent was then evaporated to give the compound **33** with a quantitative yield. The compound **33** was used to make compound **39** without further purification; ¹H NMR (CDCl₃) δ 1.54 (d, 3H), 1.79 (t, 1H, D₂O ex), 1.85 (m, 2H), 3.63 (m, 2H), 3.76 (q, 1H), 4.27 (t, 2H), 7.11-7.16(m, 2H), 7.35-7.46 (m, 4H), 7.54 (d, 2H); MS (ESI) *m/z* 325.4 (M+Na).

Compound 39 (Scheme 3). Compound **39** was prepared as described above for the preparation of compound **18**, this time employing compound **33** and TsCl. Compound **39** was purified by crystallization from ether/hexane system with a 79% yield; ¹H NMR (CDCl₃) δ 1.50 (d, 3H), 1.96 (m, 2H), 2.42 (s, 3H), 3.68 (q, 1H), 4.03 (t, 2H), 4.15 (t, 2H), 7.05-7.11 (m, 2H), 7.25-7.54 (m, 8H), 7.76 (d, 2H); ¹³C NMR

(CDCl₃) δ 18.4, 21.8, 28.4, 45.0, 50.8, 66.9, 115.2, 115.5, 123.68, 123.7, 127.9, 128.0, 129.2, 130.1, 131.0, 133.1, 135.6, 141.75, 141.8, 145.1, 158.9, 160.9, 173.9; MS (ESI) m/z 479.4 (M+Na).

5

Example 11

Compound 34 (Scheme 3). Compound **34** was prepared as described above for the preparation of compound **10**, this time employing ibuprofen (**28**) and 1,3-propanediol (**3**). After reaction, the reaction solution was washed in water and the reaction solvent was then evaporated to give compound **34** with a quantitative yield.

10 The compound **34** was used to make compound **40** without further purification; ¹H NMR (CDCl₃) δ 0.89 (d, 6H), 1.49 (d, 3H), 1.79 (t, 2H), 1.78-1.85 (m, 1H), 1.95 (t, 1H, D₂O ex), 2.45 (d, 2H), 3.53 (m, 2H), 3.71 (q, 1H), 4.22 (m, 2H), 7.09 (d, 2H), 7.26 (d, 2H).

15 **Compound 40** (Scheme 3). Compound **40** was prepared as described above for the preparation of compound **18**, this time employing compound **34** and TsCl. Compound **40** was purified by crystallization from ether/hexane system to give a white solid with a 96% yield; ¹H NMR (CDCl₃) δ 0.89 (d, 6H), 1.44 (d, 3H), 1.81-1.92 (m, 3H), 2.44 (s, 3H), 3.61 (q, 1H), 3.99 (t, 2H), 4.09 (t, 2H), 7.08 (d, 2H), 7.14 (d, 2H), 7.34 (d, 2H), 7.78 (d, 2H); ¹³C NMR (CDCl₃) δ 18.46, 21.80, 22.54, 28.39, 20 (d, 2H), 30.32, 45.16, 60.39, 66.92, 127.23, 128.04, 129.50, 130.03, 133.12, 137.68, 140.76, 145.00, 174.54; MS (ESI) m/z 441.5 (M + Na).

Example 12

25 **Compound 35** (Scheme 3). Compound **35** was prepared as described above for the preparation of compound **10**, this time employing diclofenac (**29**) and 1,3-propanediol (**3**). After reaction, compound **35** was purified by column chromatography on a silica gel column using 200:1 CH₂Cl₂/MeOH as an eluent to give the compound **35** as a white solid with a 56% yield. ¹H NMR (CDCl₃) δ 1.89 (m, 30 3H, 1H D₂O ex), 3.66 (t, 2H), 3.83 (s, 3H), 4.31 (t, 2H), 6.55 (d, 1H), 6.87 (br, 1H), 6.94-7.00 (m, 2H), 7.11-7.14 (m, 1H), 7.22-7.26 (m, 1H), 7.34 (d, 2H); MS (ESI) m/z

376.3 (M+Na).

Compound 41 (Scheme 3). Compound **41** was prepared as described above for the preparation of compound **18**, this time employing compound **35** and TsCl.

5 Compound **41** was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound **41** as a pale yellow oil and the yield was 89% ; ^1H NMR (CDCl_3) δ 2.02 (m, 2H), 2.43 (s, 3H), 3.73 (s, 2H), 4.09 (t, 2H), 4.17 (t, 2H), 6.53 (d, 1H), 6.99 (s, 1H), 6.93-7.00 (m, 2H), 7.12 (t, 1H), 7.18 (d, 1H), 7.23 (d, 1H), 7.31-7.35 (m, 3H), 7.78 (d, 2H); MS (ESI) m/z 508.3 (M).

10

Example 13

Compound 36 (Scheme 3). Compound **36** was prepared as described above for the preparation of compound **10**, this time employing carprofen (**30**) and 1,3-propanediol (**3**). After reaction, compound **36** was purified by column

15 chromatography on a silica gel column using 200:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as an eluent to give the compound **36** as a colorless oil with a 54% yield. ^1H NMR (CDCl_3) δ 1.59 (d, 3H), 1.74 (br, 1H, D_2O ex), 1.80 (m, 2H), 3.53-3.56 (m, 2H), 3.88 (q, 1H), 4.22-4.28 (m, 2H), 7.17 (d, 1H), 7.29-7.35 (m, 3H), 7.94-7.98 (m, 2H), 8.14 (br, 1H); ^{13}C NMR (CDCl_3) δ 18.99, 31.84, 46.17, 59.42, 62.10, 109.70, 111.79, 119.79, 120.21, 20 120.87, 121.92, 124.49, 125.22, 126.09, 138.24, 139.37, 140.55, 175.39; MS (ESI) m/z 332.2 (M+H).

Compound 42 (Scheme 3). Compound **42** was prepared as described above for the preparation of compound **18**, this time employing compound **36** and TsCl.

25 Compound **42** was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound **42** as a sticky oil and the yield was 90% ; The ^1H NMR (CDCl_3) δ 1.55 (d, 3H), 1.91 (m, 2H), 2.39 (s, 3H), 3.83 (q, 1H), 3.97 (t, 2H), 4.09-4.18 (m, 2H), 7.10 (d, 1H), 7.21(d, 2H), 7.32 (s, 2H), 7.38 (s, 1H)7.65 (d, 2H), 7.91 (d, 1H), 7.98 (s, 1H), 8.54 (s, 1H); ^{13}C NMR (CDCl_3) δ 18.83, 21.77, 28.32, 30 46.08, 60.59, 57.04, 109.97, 111.97, 119.58, 120.06, 120.69, 121.77, 124.38, 125.00, 125.99, 127.95, 129.22, 130.06, 132.90, 138.38, 139.19, 140.69, 145.15, 174.59; MS

(ESI) m/z 486.3 ($M + H$).

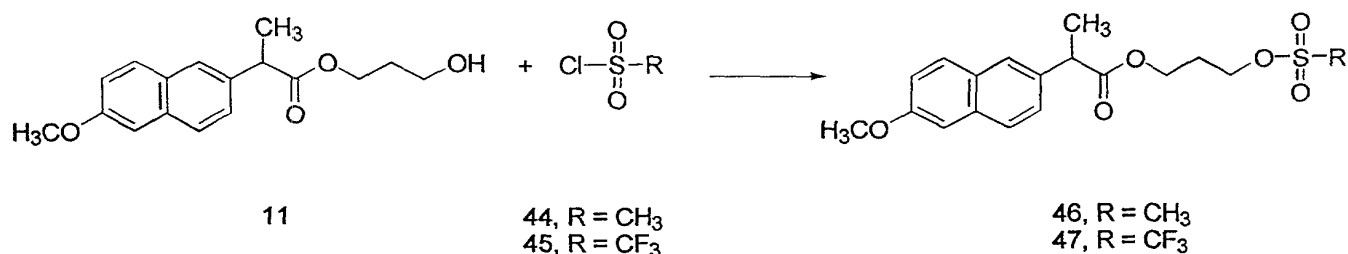
Example 14

Compound 37 (Scheme 3). Compound **37** was prepared as described above for the preparation of compound **10**, this time employing indomethacin (**31**) and 1,3-propanediol (**3**). After reaction, compound **37** was purified by column chromatography on a silica gel column using 200:1; 100:1 $CH_2Cl_2/MeOH$ as an eluents to give the compound **37** as a pale yellow oil with a 49% yield. 1H NMR, ^{13}C NMR and MS are consistent with the structure of compound **37**.

Compound 43 (Scheme 3). Compound **43** was prepared as described above for the preparation of compound **18**, this time employing compound **37** and $TsCl$. The compound **43** was purified by column chromatography on a silica gel column using hexane/ethyl acetate (3:1) as an eluent to give the compound **43** as a pale yellow oil and the yield was 71%; 1H NMR ($CDCl_3$) δ 1.97 (m, 2H), 2.36 (s, 3H), 2.44 (s, 3H), 3.63 (s, 2H), 3.83 (s, 3H), 4.05 (t, 2H), 4.15 (t, 2H), 6.66-6.68 (m, 1H), 6.87 (d, 1H), 6.93 (d, 1H), 7.33 (d, 2H), 7.47 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H); MS (ESI) m/z 592.0 ($M + Na$).

The syntheses described in Examples 15 and 16 are outlined in Scheme 4.

Scheme 4



Example 15

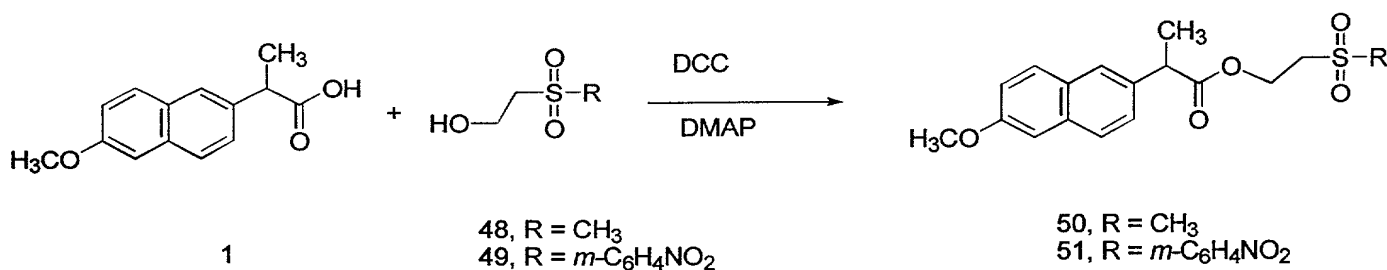
Compound 46 (Scheme 4). Compound **46** was prepared as described above for the preparation of compound **18**, this time employing compound **11** and **44**. The compound **46** was purified by crystallization from ether/hexane system to give the compound **46** as a white solid. The yield was 95%; ^1H NMR (CDCl_3) δ 1.58 (d, 3H), 2.00 (m, 2H), 2.73 (s, 3H), 3.87 (q, 1H), 3.90 (s, 3H), 4.10 (t, 2H), 4.18 (t, 2H), 7.10-7.15 (m, 2H), 7.39 (d, 1H), 7.66-7.71 (m, 3H); ^{13}C NMR (CDCl_3) δ 18.46, 28.55, 37.03, 45.56, 55.47, 55.50, 60.38, 66.36, 105.75, 119.32, 126.09, 126.27, 127.44, 129.06, 129.41, 133.89, 135.68, 157.91, 174.59; MS (ESI) m/z 388.5 ($\text{M} + \text{Na}$).

Example 16

Compound 47 (Scheme 4). Compound **47** is prepared as described above for the preparation of compound **18**, this time employing compound **11** and compound **45**. The compound is purified by crystallization and the yield was 70-90%. The ^1H NMR, ^{13}C NMR and MS are consistent with the structure of compound **47**.

The syntheses described in Examples 17 and 18 are outlined in Scheme 5.

Scheme 5



Example 17

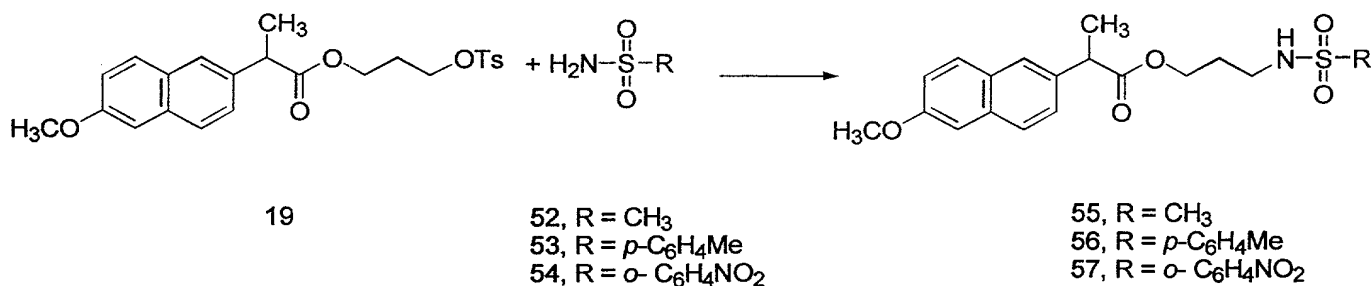
Compound 50 (Scheme 5). To a solution of naproxen (**1**) (1.15g, 5 mmol), compound **48** (0.62g, 5 mmol) and dimethylamino pyridine (DMAP) (0.12g, 1 mmol) was added dicyclohexyldicarbodiimide (DCC) (1.03g, 5 mmol) at 0° C. The resulting solution was stirred at 0° C for 1.5 h. After reaction, the solid was filtered off and the solvent was evaporated. The residue was washed with ether to give 1.4g (83%) of compound **50** as a white solid; ¹HNMR (CDCl₃) δ 1.59 (d, 3H), 2.38 (s, 3H), 3.17 (m, 2H), 3.87 (q, 1H), 3.92 (s, 3H), 4.43 (m, 1H), 4.59 (m, 1H), 7.10 (d, 1H), 7.15 (m, 1H), 7.33 (m, 1H), 7.67 (d, 1H), 7.70 (m, 2H); MS (ES) *m/e* 358.2 (M+Na).

Example 18

Compound 51 (Scheme 5). Compound **51** was prepared as described above for the preparation of compound **50**, this time employing compound **1** (1.15g, 5mmol) and **49** (1.16g, 5 mmol). The compound was purified by column chromatography on a silica gel column using 1:1 hexanes/ethyl acetate as eluent to give 0.91g of compound **51** as a pale yellow oil; ¹H NMR (CDCl₃) δ 1.45 (d, 3H), 3.48 (m, 2H), 3.59 (q, 1H), 3.92 (s, 3H), 4.47 (m, 2H), 7.10 (d, 1H), 7.18 (m, 2H), 7.45 (s, 1H), 7.49 (t, 1H), 7.65 (t, 2H), 8.06 (q, 1H), 8.28 (q, 1H), 8.68 (s, 1H); ¹³C NMR (CDCl₃) 18.8, 45.2, 55.4, 55.5, 57.9, 105.8, 123.6, 125.9, 127.5, 128.4, 129.0, 129.3, 130.8, 133.7, 133.9, 134.9, 141.5, 148.4, 158.0, 174.0.

The syntheses described in Examples 19-21 are outlined in Scheme 6.

Scheme 6



Example 19

Compound 55 (Scheme 6). A mixture of compound **19** (2.2g, 5 mmol), compound **52** (0.57g, 6mmol) and K_2CO_3 (3.45g, 25 mmol) in 50 ml of dimethyl formamide (DMF) was stirred for a week. The reaction solution was poured into 100 ml of water and extracted with CH_2Cl_2 . The organic phase was washed with water (50 x 5) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography on a silica gel column using 3:1 hexane/ ethylacetate as an eluent to give 0.3g (16%) of compound **55** as a pale yellow oil; 1H NMR ($CDCl_3$) δ 1.60 (d, 3H), 2.38 (s, 3H), 3.17 (m, 2H), 3.87 (q, 1H), 3.92 (s, 3H), 4.45 (m, 1H), 4.59 (m, 1H), 7.10 (s, 1H), 7.14-7.16 (q, 1H), 7.32-7.35 (q, 1H), 7.62 (s, 1H), 7.67-7.71 (m, 2H); MS (ESI) m/z 358.2 (M + Na).

Example 20

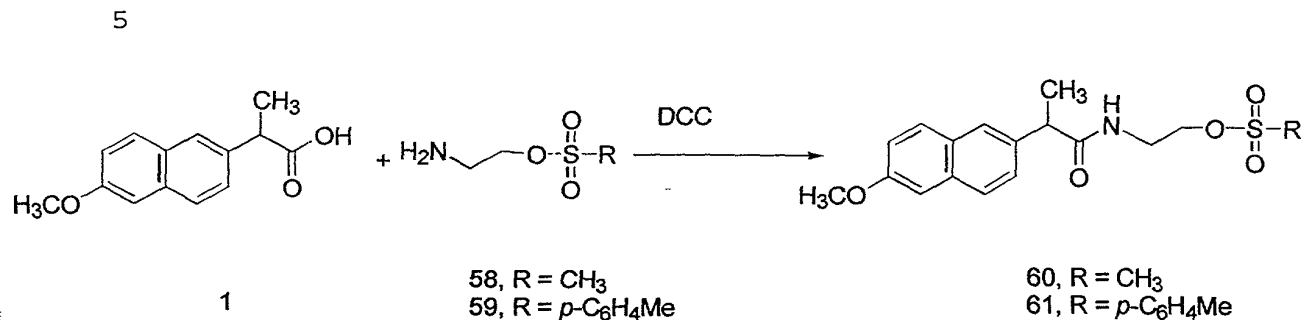
Compound 56 (Scheme 6). Compound **56** was prepared as described above for the preparation of compound **55**, this time employing compound **19** and compound **53**. The compound was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give compound **56** as a pale yellow oil (33%). 1HNMR ($CDCl_3$) δ 1.54 (d, 3H), 1.72 (m, 2H), 2.83 (m, 2H), 3.80 (q, 1H), 3.92 (s, 3H), 4.10 (t, 2H) 7.07-8.10 (m, 10H); MS (ESI) m/z 442.3 (M + H).

Example 21

Compound 57 (Scheme 6). Compound **57** was prepared as described above for the preparation of compound **55**, this time employing compound **19** and compound **54**. The compound was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give compound **57** as a pale yellow oil (11%). The 1HNMR ($CDCl_3$) δ 1.55 (d, 3H), 1.80 (m, 2H), 3.03 (m 2H), 3.86 (m, 1H), 4.13 (m, 2H), 7.07-7.93 (m, 10H); MS (ESI) m/z 473.4 (M + H).

The syntheses described in Examples 22 and 23 are outlined in Scheme 7.

Scheme 7



15

Example 22

Compound 60 (Scheme 7). Compound **60** is prepared as described above for the preparation of compound **50**, this time employing naproxen **1** and compound **58**. After reaction the compound is purified by column chromatography on a silica gel column to give the compound **60** in a yield from 75 –95%.

20

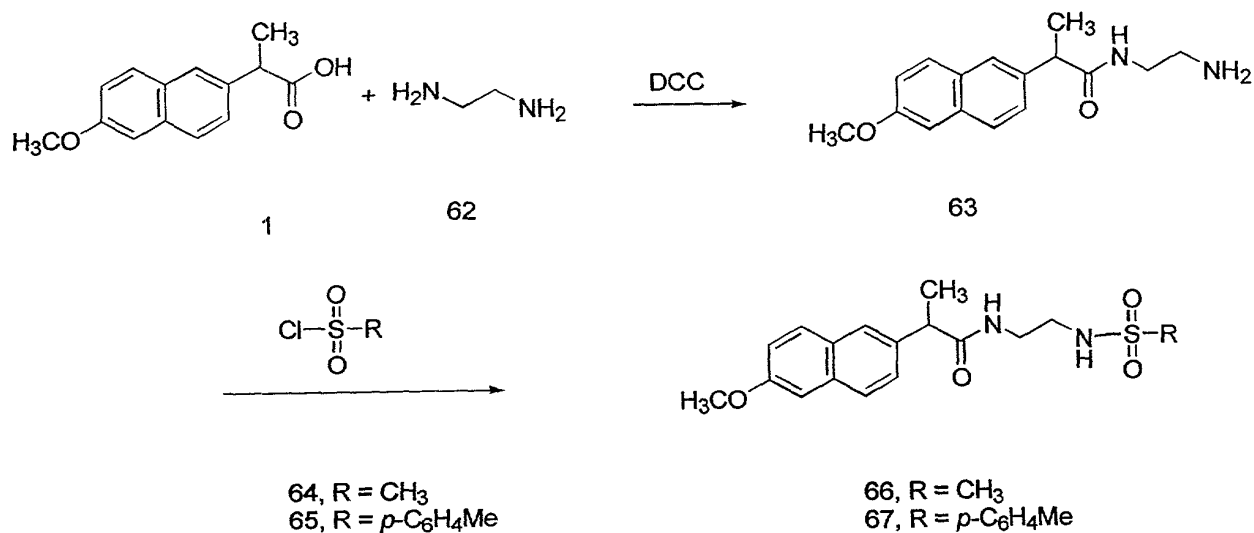
Example 23

Compound 61 (Scheme 7). Compound **61** is prepared as described above for the preparation of compound **50**, this time employing naproxen (**1**) and compound **59**. After reaction, the compound is purified by column chromatography on a silica gel column to give compound **61** in a yield from 75 –95%.

25

The syntheses described in Examples 24 and 25 are outlined in Scheme 8.

Scheme 8



Example 24

Compound 63 (Scheme 8). Compound **63** is prepared as described above for the preparation of compound **50**, this time employing naproxen (**1**) and compound **62**. After reaction, the compound is purified by column chromatography on a silica gel column to give compound **63** in a yield of 75–95%.

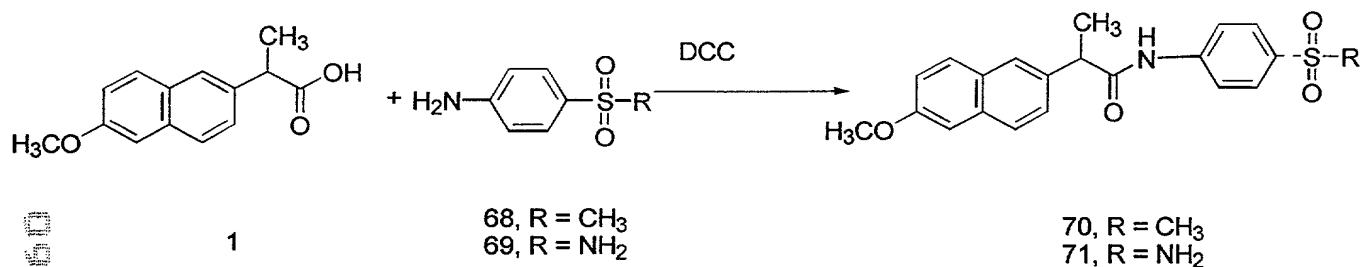
Compound 66 (Scheme 8). Compound **66** is prepared as described above for the preparation of compound **18**, this time employing compound **63** and compound **64**.

Example 25

Compound 67 (Scheme 8). Compound **67** is prepared as described above for the preparation of compound **18**, this time employing compound **63** and compound **65**.

The syntheses described in Examples 26 and 27 are outlined in Scheme 9.

Scheme 9



15

Example 26

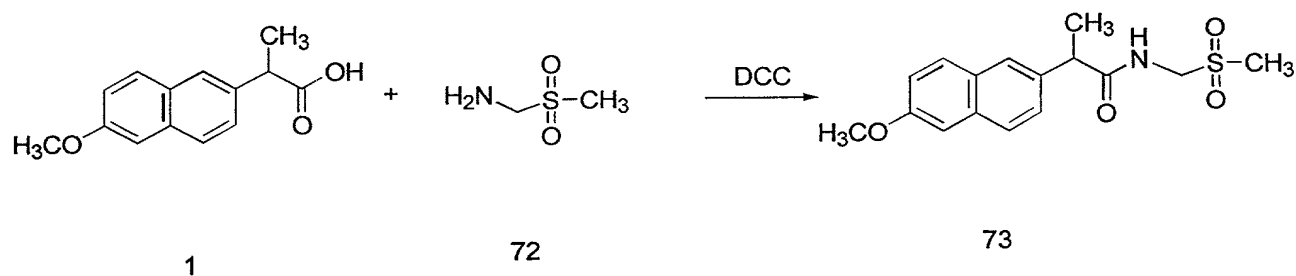
20 **Compound 70** (Scheme 9). Compound **70** is prepared as described above for the preparation of compound **60**, this time employing compound **1** and compound **68**.

Example 27

Compound 71 (Scheme 9). Compound **71** is prepared as described above for the preparation of compound **60**, this time employing compound **1** and compound **69**.

The synthesis described in Example 28 is outlined in Scheme 10.

Scheme 10

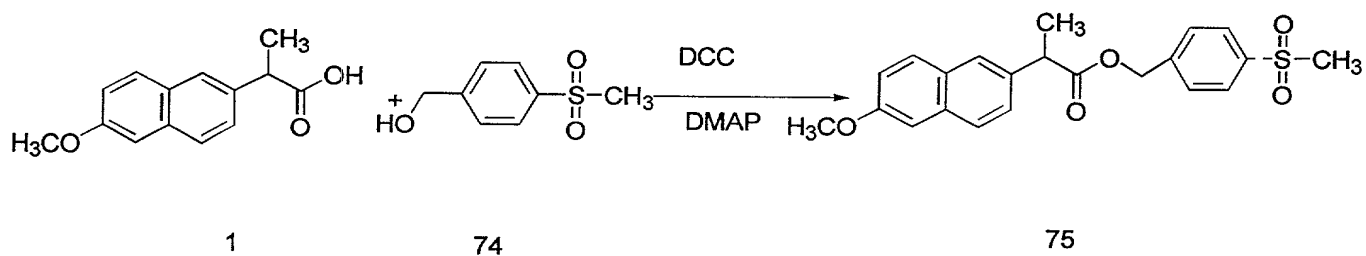


Example 28

Compound 73 (Scheme 10). Compound 73 is prepared as described above for the preparation of compound 60, this time employing compound 1 and compound 72.

The synthesis described in Example 29 is outlined in Scheme 11.

Scheme 11



Example 29

Compound 75 (Scheme 11). Compound 75 is prepared as described above for the preparation of compound 60, this time employing compound 1 and compound 74.

Example 30

5 Reduced numbers of intestinal ulcers in rat acute and subacute enteropathy
 models by the invention modified NSAID (compound 19), a prodrug of naproxen

NSAIDs are important drugs used to treat acute and chronic inflammation as well as pain and fever. The major limitation to NSAID use is the occurrence of gastrointestinal ulcers and erosions. These side effects are produced by a combination
10 of local and systemic effects. Attempts have been made to circumvent the local side effects of NSAIDs by making them as prodrugs, which will bypass the stomach, but so far this has not been clearly successful. It is demonstrated here that the invention modified NSAIDs substantially reduce GI toxicity, while exhibiting dose equivalent efficacy in anti-inflammation activity in both acute and chronic inflammation animal
15 models.

Sprague-Dawley rats (male, 150 - 200 g), were orally dosed once daily for either 3 days (acute model) or 14 days (subacute model). Twenty-four hours after the last dose, the rats were injected i.v. with Evans Blue (5 ml/kg, 10 mg/ml) to stain the
20 ulcers. Ten to twenty minutes later the animals were sacrificed by CO₂ inhalation and the intestines removed, opened lengthwise and the contents removed. The long dimensions of all ulcers were measured using a ruler and summed to give a total ulcer score.

25 In the acute model (Figure 1), ulceration after dosing with an invention modified NSAID (compound 19) was 15% of that seen with an equimolar dose of naproxen. PEG had no ulcerogenic effect. In the subacute model (Figure 2), ulceration was less than 5% of that seen with a corresponding dose of naproxen at all three doses used. Again, PEG had no effect. These results suggest that invention
30 modified NSAIDs are much less ulcerogenic than naproxen.

Example 31

Reduction of chronic hindlimb inflammation in the rat adjuvant arthritis model by the invention modified NSAID (compound 19), a prodrug of naproxen

5 NSAIDs are useful in the treatment of both chronic and acute inflammatory conditions. Efficacy in chronic inflammation can be estimated using the rat adjuvant arthritis model. In this model Lewis male rats (175-250 g) are injected intradermally in the footpad with M. tuberculosis powder suspended in mineral oil at 5 mg/ml. Progressive swelling of the uninjected paw and ankle joint between days 5 and 15 is measured by plethysmometry.

Rats were dosed daily by oral gavage with 5 ml/kg of naproxen at 3 to 30 mg/kg in phosphate buffered saline (PBS) and with equimolar doses of an invention modified NSAID at 1 ml/kg in PEG 300. The results (Figure 3) show that the invention modified NSAID resulted in antiinflammatory effects comparable to those of naproxen in this model.

Example 32

Reduction of acute hindlimb inflammation in the rat carrageenan-induced hindlimb edema model by the invention modified NSAID (compound 19), a prodrug of naproxen

Efficacy of NSAIDs in acute inflammation can be estimated by using intraplantar injection of carrageenan in the rat. Sprague-Dawley rats (200-250 g male) are injected intradermally in the footpad with 50 μ l of a 1% carrageenan solution in PBS. Swelling of the injected paw is measured 3 & 4 hours later, using a plethysmometer.

Pretreatment with oral naproxen one hour before the carrageenan injection at 10 mg/kg resulted in an approximately 50% reduction in swelling at both time points (Table 1). An equimolar dose of an invention modified NSAID reduced inflammation to the same degree at both time points. These results suggest that invention modified NSAIDs are comparable in effect to naproxen at 10 mg/kg.

Table 1. Effects of naproxen and the invention modified NSAID (compound 19) on paw volume increase in carrageenan-induced inflammation in rats.

Treatment	4 Hours	5 Hours
Vehicle	0.73 ± 0.10	0.85 ± 0.10
Naproxen (1 mg/kg)	0.63 ± 0.07	0.75 ± 0.08
Naproxen (10 mg/kg)	$0.32 \pm 0.05^*$	$0.39 \pm 0.07^*$
Compound 19 (1.75 mg/kg)	0.78 ± 0.04	0.93 ± 0.04
Compound 19 (17.5 mg/kg)	$0.34 \pm 0.06^*$	$0.40 \pm 0.06^*$

5 * P < 0.05 vs Vehicle by unpaired t-test.

Invention modified NSAIDs are seen to have antiinflammatory activity similar to naproxen in the chronic adjuvant arthritis and acute carrageenan hindlimb edema rat models. The tendency to cause intestinal ulcers is reduced substantially invention modified NSAID. Thus, invention modified NSAIDs provide an effective prodrug form of naproxen with reduced intestinal side effects.

Example 33

15 Plasma pharmacokinetics of naproxen and the invention modified NSAID after oral administration in rats

The invention compound (compound 19) is a naproxen prodrug, which is a conjugate of naproxen and tosylate. Oral administration of the invention compound resulted in the release of free naproxen. The pharmacokinetics of naproxen release from the invention modified NSAID and its parent drug, naproxen, was evaluated in rats after oral administration.

25 The carotid artery of Sprague-Dawley rat (250-350 g, male) was catheterized at least one day before drug administration and flushed with 30% polyvinyl pyrrolidone (PVP) (400 U/mL of heparin) to maintain patency. At predetermined time points (see Table 2), blood samples (250 μ L) were collected by unhooking the flushing syringe and letting the blood flow out of the catheter and into the centrifuge

tubes. After centrifugation (13,000 rpm, 10 min, 4°C), the plasma samples were collected and analyzed in the same day.

Table 2: Rat group assignment and doses

Test Article	Group #	Rat #	Dose* (mg/kg)	Sample Time
Naproxen	1	1, 2, 3, & 4	Oral (2 mg/kg)	5 min, 0.5, 1, 4, 7, 10, 13, 16, 19, 22, & 24 hrs
Invention Compound 19	2	5, 6, 7, & 8	Oral (2 mg/kg)	15 min, 0.5, 1, 3, 5, 6, 7, 8, 22, 23, & 24 hrs

*Indicates amount of naproxen in dose.

Aliquot of plasma sample (100 μ L) was mixed with 200 μ L of acetonitrile. After vortexing and centrifugation (13,000 rpm, 10 min, 4°C), 200 μ L of supernatant was removed and added to 300 μ L of a 58:42 mixture of 50 mM phosphate buffer (pH 5.0) and acetonitrile. Following vortexing and centrifugation, 25 μ L of supernatant was removed and analyzed by HPLC with a UV detection system.

The average plasma concentration at each time point was calculated and utilized in a pharmacokinetic analysis. Noncompartmental pharmacokinetic analysis was carried out using WinNolin (Pharsight, Mountainview, California) to calculate the maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve from zero to the last time point (AUC_{last}), the area under the curve from zero to infinite time (AUC_{inf}), and the terminal phase half life ($Beta-t_{1/2}$).

The AUC_{all} , AUC_{INF} , and $t_{1/2}$ of naproxen from naproxen and a modified form of naproxen according to the invention were found to be similar (Table 3). On the other hand, for the invention modified form of neproxen, the C_{max} was lower and the T_{max} longer, compared to naproxen (see Table 3).

Table 3 - Non-Compartmental Pharmacokinetic Analysis of naproxen and the invention modified form of naproxen according to the (compound 19) after oral administration in rats

5

Drug	Dose*	C _{max}	T _{max}	AUC _{all}	AUC _{INF}	t _{1/2}	N
	(mg/kg)	(µg/mL)	(hrs)	(µg*hr/mL)		(hrs)	
Naproxen	2	7.77±4.13	0.5±0.5	50±6	55±7	6.2±0.4	4
Invention modified naproxen	2	3.87±1.05	6.8±1.5	49±10	56±14	6.8±2.7	4

*Indicates amount of naproxen in dose.

10 Following oral naproxen administration, the naproxen plasma levels were at the highest at the first time-point (5 minutes) then declined in a bi-exponential manner. In contrast, after oral administration of a modified form of naproxen according to the invention, the maximum naproxen levels were observed at a much later time (T_{max} of 6.8±1.5 hrs). The similar AUC_{all}, AUC_{INF}, and T_{1/2} values but lower

15 C_{max} and longer T_{max} values supports the conclusions drawn from the results obtained from pharmacological studies, i.e. that a modified form of naproxen according to the invention conjugate has equivalent pharmacological efficacy and greatly improved gastrointestinal safety profile compared to naproxen.

20 While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A compound having the structure:

5

X-L-Z

wherein:

X = a non-steroidal anti-inflammatory drug (NSAID),

L = an optional linker/spacer,

10

Z = a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

2. A compound according to claim 1 wherein said NSAID is

15

acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenprofen calcium, flurobiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, or flosulide.

20

3. A compound according to claim 2 wherein said NSAID is naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, or carprofen.

4. A compound according to claim 1 wherein the sulfur-containing

25

functional group is sulfonate, reverse sulfonate, sulfonamide, reverse sulfonamide, sulfone, sulfinate, or reverse sulfinate.

5. A compound according to claim 4 wherein the sulfur-containing functional group is sulfonate or reverse sulfonate.

5 7. A compound according to claim 6 wherein said aromatic sulfonate is tosylate or brosylate.

10

10. A compound according to claim 4 wherein the sulfur-containing
15 functional group is a sulfone.

20 12. A compound according to claim 11 wherein said sulfone is methyl sulfone, ethyl sulfone.

25

15. A compound according to claim 4 wherein the sulfur-containing
30 functional group is a sulfonamide or reverse sulfonamide.

16. A compound according to claim 15 wherein the sulfur-containing functional group is an optionally substituted C₁ to C₁₀ alkyl sulfonamide.

17. A compound according to claim 16 wherein the sulfur-containing functional group is methyl sulfonamide.

18. A compound according to claim 15 wherein the sulfur-containing functional group is an optionally substituted aromatic sulfonamide.

19. A compound according to claim 18 wherein the sulfur-containing functional group is toluene sulfonamide.

20. A compound according to claim 4 wherein the sulfur-containing functional group is a sulfinic acid or reverse sulfinic acid.

21. A compound according to claim 1 wherein L, when present, has the structure:

W-R-

wherein:

20 R is optional, and when present is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

25 W is ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, imine or enamine.

22. A formulation comprising a compound according to claim 1 in a pharmaceutically acceptable carrier therefor.

007290-8820960

23. A formulation according to claim 22 wherein said pharmaceutically acceptable carrier is a solid, solution, emulsion, dispersion, micelle or liposome.

5 24. A formulation according to claim 22 wherein said pharmaceutically acceptable carrier further comprises an enteric coating.

25. In a method for the administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject for the treatment of a pathological condition, the
10 improvement comprising directly or indirectly covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

26. The method of claim 25 wherein said pathological condition is septic
15 shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease, diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis,
20 uveitis, ileitis, inflammation, burn, infection, hemodialysis, chronic fatigue syndrome, stroke, cancers, cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease,
25 chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors, malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease,
30 drug-induced lung injury, myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, or coronary artery disease.

27. In the treatment of a subject suffering from a pathological condition by administration thereto of a non-steroidal anti-inflammatory drug (NSAID), the improvement comprising covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

28. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject an effective amount of a non-steroidal anti-inflammatory drug (NSAID),
wherein said NSAID is effective for treatment of said condition, and
wherein said NSAID has been modified by the direct or indirect covalent attachment thereto of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

29. A method for the preparation of a protected form of a non-steroidal anti-inflammatory drug (NSAID), said method comprising directly or indirectly covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID.

30. A method according to claim 29 wherein said NSAID is acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenprofen calcium, flurbiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, or flosulide.

31. A method for reducing the side effects induced by administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject, said method comprising directly or indirectly covalently attaching a sulfur-containing functional group
5 containing an optionally substituted hydrocarbyl moiety to said NSAID prior to administration to said subject.

32. A method for enhancing the effectiveness of a non-steroidal anti-inflammatory drug (NSAID), said method comprising directly or indirectly covalently
10 attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID.

33. A method for the prevention or treatment of an inflammatory or infectious disease in a subject in need thereof, said method comprising administering to
15 said subject an amount of the compound of claim 1 effective to alleviate said condition.

ABSTRACT

5

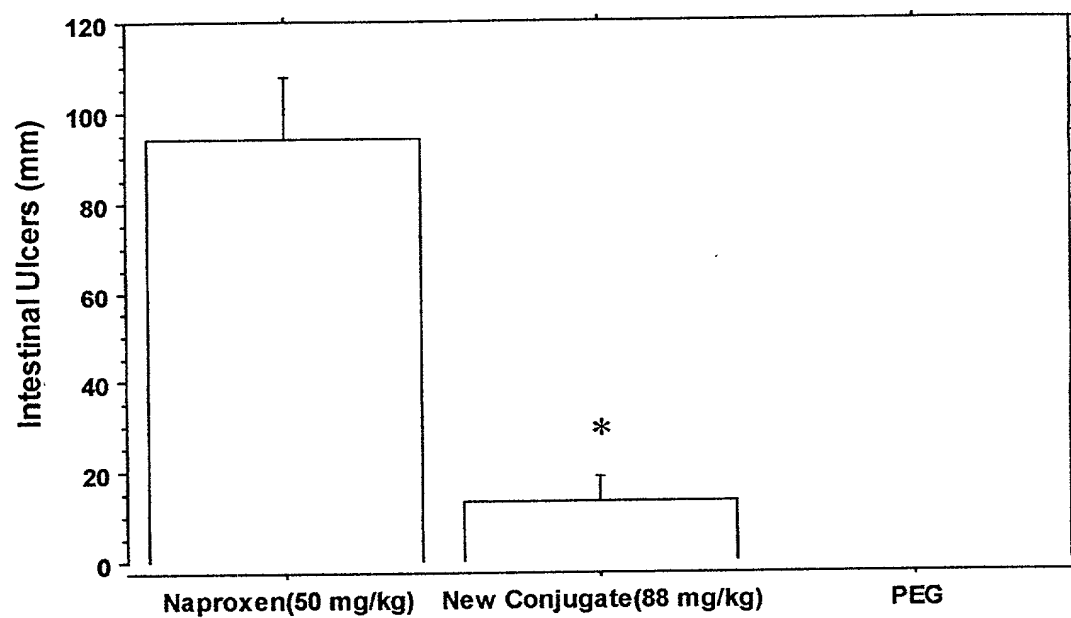


FIGURE 1

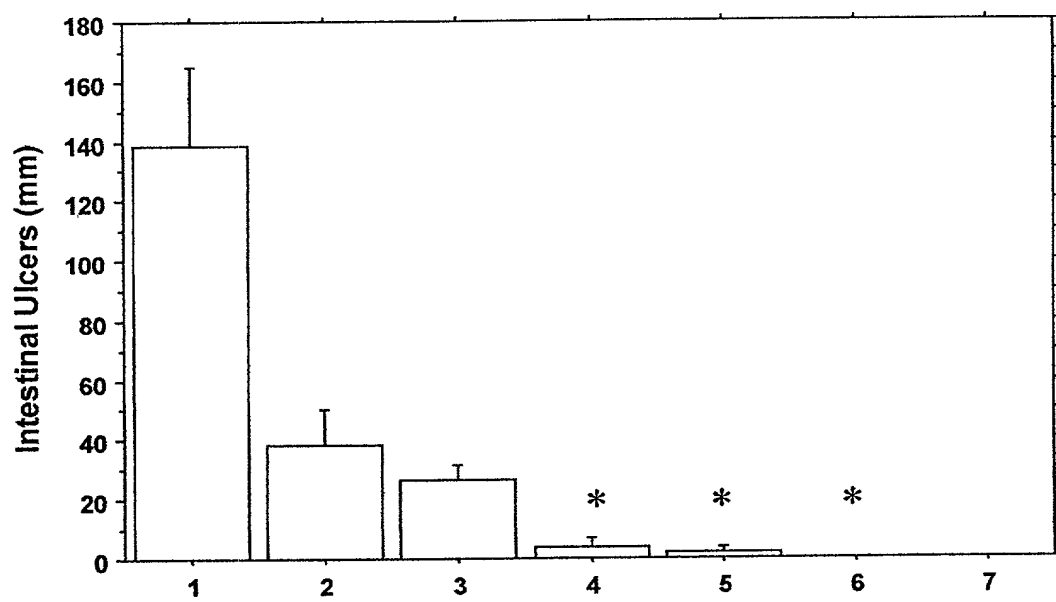


FIGURE 2

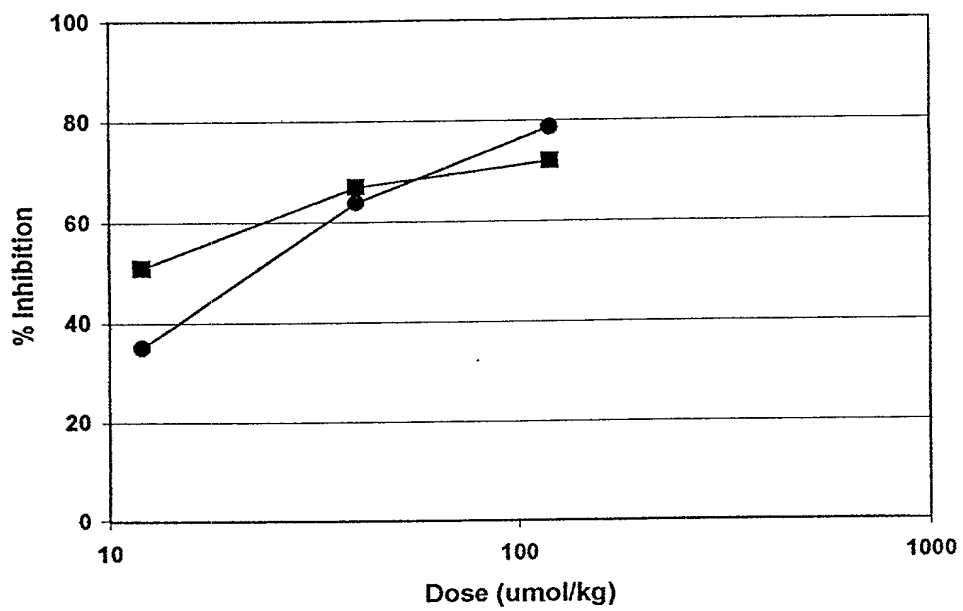


FIGURE 3

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name.

I believe that I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled **PROTECTED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR**, the specification of which

 X is attached hereto. (Attorney Docket No. MEDIN1400)
 X was filed on June 23, 2000 as U.S. Application
Serial No. and
was amended on if applicable

I hereby authorize and request insertion of the application serial number of the Application when officially known.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, Code of Federal Regulations ("C.F.R."), § 1.56.

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)

(Filing Date)

With respect to the Application, I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of the application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability of the subject matter of the Application as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of the Application:

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: Ching-San Lai

Inventor's signature: 

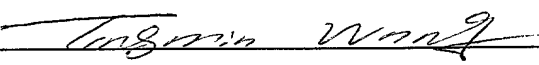
Date: 6/23/2000

Residence: Encinitas, California

Citizenship: United States

Post Office Address: 209 Lolita Street
Encinitas, CA 92024

Full name of second inventor: Tingmin Wang

Inventor's signature: 

Date: 6/23/00

Residence: San Marcos, CA

Citizenship: People's Republic of China

Post Office Address: 585 Sonoma Street
San Marcos, CA 92069

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Lai and Wang
Application No.:
Filed: June 23, 2000
Title: PROTECTED FORMS OF A COMBINATION OF
PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR

POWER OF ATTORNEY BY ASSIGNEE

As a below-named assignee of the above-identified application ("Application"):

I hereby appoint the following attorneys of the assignee to prosecute the
Application and to transact all business in the United States Patent and Trademark Office
connected therewith:

JOSEPH R. BAKER
TIM ELLIS
LISA A. HAILE
WILLIAM N. HULSEY III,
RICHARD J. IMBRA
SHEILA R. KIRSCHENBAUM
JUNE M. LEARN
TIMOTHY W. LOHSE
TERRANCE A. MEADOR
JOHN OSKOREP
STEPHEN E. REITER
STEVEN R. SPRINKLE
RAMSEY R. STEWART
DAVID R. STEVENS
BARRY N. YOUNG

Registration No. 40,900
Registration No. 41,734
Registration No. 38,347
Registration No. 33,402
Registration No. 37,643
Registration No. 44,835
Registration No. 31,238
Registration No. 35,255
Registration No. 30,298
Registration No. 41,234
Registration No. 31,192
Registration No. 40,825
Registration No. 38,322
Registration No. 38,626
Registration No. 27,744

Applicant: Lai and Wang
Application No.:
Filed: June 23, 2000
Page 2

**I hereby authorize and request insertion of the application number of the
Application when officially known.**

Direct all telephone calls to:

STEPHEN E. REITER
Telephone: (858) 677-1409

Address all correspondence to:

STEPHEN E. REITER
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, CA 92121

MEDINOX, INC., a corporation of the state of California.

By: _____

Name: _____

Ching-San Lai

Title: _____

President and Chief Executive Officer

Date: _____

6/23/2000